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Summary

The present thesis aims at identifying the neurobiological features that characterize major depressive disorder (MDD) and depression in Alzheimer's disease (AD). Depression occurs in 20-50% of the AD patients. The underlying question is to what extent depression in AD shares its biological characteristics with MDD. This question is addressed within the framework of the hypothalamic-pituitary-adrenal (HPA)-axis hypothesis of depression. Different components of the HPA- or stress-axis are studied both in depressed subjects (vasopressin and oxytocin) and in Alzheimer patients with and without depression (cortisol, corticotropin-releasing hormone (CRH), vasopressin and oxytocin). In addition, the relationship between depressive symptomatology and the neuropathological hallmarks of AD, i.e. plaques and tangles, is determined.

Hypothalamic changes in major depressive disorder

Elevated vasopressin plasma levels have been reported in MDD, particularly in relation to its melancholic subtype, and to suicidal behaviour. Two hypothalamic structures produce plasma vasopressin: the supraoptic nucleus (SON) and the paraventricular nucleus (PVN). It was not known which of these structures is responsible for the increased vasopressin plasma levels in depression. Previously, increased vasopressin neuron numbers in the PVN had been found in depressed subjects compared to controls. Hypothalamic vasopressin potentiates the effect of CRH on the pituitary to release adrenocorticotrophic hormone (ACTH). Vasopressin, therefore, is a factor in HPA-axis regulation. In order to determine the origin of the increased vasopressin plasma levels in depression, and especially its melancholic subtype, we measured the amount of vasopressin mRNA in the PVN and SON of depressed patients and controls by in situ hybridization, putting special emphasis on the distinction of melancholic and non-melancholic type depression. In the SON, a 60% increase of vasopressin mRNA expression was observed in depressed patients compared to controls ($p=0.02$). In the PVN, too, an increase was observed, but this was not significant. However, in the melancholic subgroup vasopressin mRNA expression was significantly increased in both the

SON ($p=0.01$) and the PVN ($p=0.028$) compared to controls. Our findings of increased vasopressin gene expression in depressed subjects points to the SON as the main source of elevated vasopressin plasma levels in depression. Moreover, whereas so far the PVN was the focus of hypothalamic HPA-axis research, the results point to the SON as a factor in stress-axis activation in depression. In addition, our data indicate that the increase in hypothalamic vasopressin mRNA expression is particularly relevant in melancholic-type depression, which is in accordance with earlier studies that found elevated vasopressin plasma levels to be related to melancholic-type depression.

Vasopressin differs only two aminoacids from oxytocin, a neuropeptide with many effects in social interactions. Both neuropeptides are released from the PVN and SON, but whereas vasopressin potentiates HPA-axis activity, animal experiments have shown that oxytocin attenuates the stress-induced activity of the HPA-axis in various species, including humans, and that oxytocin inhibits HPA-axis activity under basal conditions. At the same time, oxytocin seems to be essential for an adequate ACTH response under stressful conditions. Previously, the number of oxytocin neurons in the PVN was found to be increased in depressed subjects. In the same group of depressed patients in which we determined vasopressin mRNA in the SON, we also measured the amount of oxytocin mRNA, by in situ hybridization. A significant increase of oxytocin mRNA was found in the PVN in melancholic type patients compared to non-melancholic-type patients ($p=0.038$), while melancholic-type patients compared to controls showed a trend ($p=0.099$) towards higher oxytocin mRNA levels in the PVN. There was, however, no difference in oxytocin mRNA in either the PVN or SON when the entire group of depressed patients was compared with control subjects. Interestingly, in depressed subjects, a correlation existed between the amount of vasopressin mRNA and the amount of oxytocin mRNA in the PVN ($\rho=0.9$, $p=0.002$) and SON ($\rho=0.7$, $p=0.02$), while in controls such a correlation was only found in the SON ($\rho=0.8$, $p=0.021$). The observed increase in oxytocin mRNA in melancholic-type depression may be related to specific symptoms of this type of depression, like weight loss and loss of appetite, since oxytocin is a satiety peptide. In support of this hypothesis we found the highest amount of oxytocin mRNA in a melancholically depressed subject, whose medical record mentioned 16 kg weight loss in the depressive episode that occurred during the last year of her life.

In depressed subjects, the increases of vasopressin and oxytocin in the PVN and SON seem to be related since a correlation existed between the amount of vasopressin mRNA and the amount of oxytocin mRNA both in the PVN and in the SON. Consequently, a differential expression of vasopressin and oxytocin

in the PVN and SON does not seem to take place. Rather, in melancholic-type depression both vasopressin and oxytocin expression are increased in both nuclei. However, due to the relatively small patient groups we did not always find a significant difference in either of the nuclei. In general, our data suggest that increased hypothalamic expression of vasopressin is especially related to melancholic-type depression.

Depression in Alzheimer's disease

HPA-axis hyperactivity is well established, not only in MDD but also in AD, resulting in, e.g., increased cerebrospinal fluid (CSF) cortisol levels. Assuming that depression in AD has the same pathophysiological characteristics as MDD, one could hypothesize that HPA-axis activity is even more increased in depressed Alzheimer patients than in non-depressed Alzheimer patients, resulting in higher CSF cortisol levels. To test this hypothesis, cortisol levels were measured in post mortem CSF of depressed and non-depressed Alzheimer patients and of controls. The Alzheimer patients participated in a prospective study of depression in AD. We used DSM-classification and, amongst other scales, the Cornell scale for depression in dementia to measure depressive symptoms. This scale was specially designed as a quantitative measure for depression symptoms in all stages of dementia. The patients underwent a clinical evaluation every six months during the last years of their lives. A systematic neuropathological evaluation was performed post mortem and the extension of the Alzheimer changes was established according to the Braak stage for tangles. Moreover, a neuropathologist performed a differentiated semi-quantitative evaluation of the density of the Alzheimer lesions (neuritic plaques and neurofibrillary tangles throughout the neocortex). The Alzheimer patients described in our studies participated in this cohort. We found that the post mortem CSF cortisol levels in Alzheimer patients were more than double those of controls, which is in accordance with earlier studies, while no significant differences were found between depressed and non-depressed Alzheimer patients. Our interpretation of these results is that they suggest a different pathophysiology in depression in AD compared to MDD.

In MDD a fourfold increase of the number of CRH immunoreactive neurons in the PVN, which constitute the starting point of the HPA-axis, had already been found. We aimed to find out whether in depression in AD this same phenomenon - an increased CRH neuron number - could be observed. Twenty-three hypothalami were used from Alzheimer patients from the same cohort as described above. The number of CRH neurons was determined using immunocytochemistry and the Image Pro Plus analysis-program. We found a

significant positive correlation between the Cornell scores and the number of CRH neurons in Alzheimer patients ($p=0.039$). In addition, and in accordance with earlier findings, no difference was found between Alzheimer patients as a group compared to controls. Our results suggest that MDD and depression in AD share, at least partly, their hypothalamic pathophysiological characteristics.

Vasopressin and oxytocin, produced in the PVN and SON, are considered to be involved in the pathophysiology of MDD. While it was previously shown that in AD the vasopressin mRNA levels in the PVN and SON are unchanged, oxytocin mRNA in both nuclei was never measured before in AD. We therefore determined whether vasopressin and oxytocin expression are changed in depression in AD. Post mortem brain tissue was obtained from the same 23 patients described above and the amount of vasopressin and oxytocin mRNA in the PVN and SON was determined by *in situ* hybridization. The group of Alzheimer patients did not differ significantly from the 6 control subjects with respect to the amount of vasopressin or oxytocin mRNA in the PVN or SON. Also, no significant difference was found between the depressed and non-depressed Alzheimer patients with respect to the amount of vasopressin or oxytocin mRNA in either the PVN or SON. In addition, no significant relationship was found between the Cornell score and vasopressin or oxytocin mRNA in these nuclei. The results of this study indicate that in depression in AD vasopressin and oxytocin gene expression at the level of the PVN and SON are unchanged. For vasopressin, this means a difference with MDD. In addition, we found an unaltered oxytocin mRNA expression in both nuclei in AD.

Neuritic plaques and tangles, the neuropathological hallmarks of AD, were reported to be related to a life-time history of depression, while it was previously found that no relationship existed between depressive symptoms and Alzheimer pathology. However, in this study no appropriate diagnostic instrument was used to determine depressive symptoms in demented subjects. Since there is a profound overlap of symptoms between depression and AD, the use of such an instrument is essential in these kinds of studies. Therefore, in our study we used the Cornell scale for depression in dementia. We determined in Alzheimer patients whether there would also be a relationship between depressive state and the neuropathological hallmarks of AD, while controlling for clinical severity of dementia. In total, the brains of 43 Alzheimer patients were obtained from the prospective study of depression in AD. From all patients the last clinical evaluations prior to death, together with post mortem neuropathology measures, were analysed. We found a significant correlation between the Cornell scores and the sum score for the density of neuritic plaques in the entire cortex ($p=0.027$), and in particular in the temporal cortex ($p=0.012$). The observed correlations

were independent of sex, age, clinical dementia severity and duration of AD. This study shows a positive relationship between depressive state at the time of death and the presence of neuritic plaques in AD, which was independent of the clinical severity of dementia. Since neuritic plaques are not present in MDD, at first sight this finding points in the direction of a different pathophysiology of MDD and depression in AD. However, the relationship between neuritic plaques and depressive symptoms may be explained by a pathophysiology shared by both disorders, such as the HPA-axis activation, as suggested by our finding of an increased CRH neuron number.

Conclusion

The central research question of this thesis was to what extent depression in AD shares its biological characteristics with MDD. We approached this issue from the perspective of the HPA-axis hypothesis of depression. In both conditions the results indicated a similar pathophysiological change of increased activity at the level of CRH neurons in the PVN. In addition, they showed that depressive symptoms in AD are related to the density of neuritic plaques. Regarding vasopressin and oxytocin mRNA expression in the PVN and SON, we found no changes in depression in AD, whereas we did find an increased level of vasopressin mRNA in the SON in MDD. In the melancholic subtype of MDD, an increase in vasopressin mRNA was found in both the PVN and the SON. For oxytocin mRNA we found an increase in the PVN in melancholic-type versus non-melancholic-type depressed patients. Our results draw attention to the possible importance of vasopressin as a pathophysiological factor in MDD, and to the SON as the main source of this vasopressin. In addition, they provide further ground to the distinction between melancholic-type depression and non-melancholic-type depression when evaluating molecular changes in the brain. This thesis aims to contribute to the development of new therapeutic strategies for MDD and depression in AD, targeting the release and effects of hypothalamic neuropeptides, especially CRH and vasopressin.